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10/661,049	09/12/2003	Richard D. Cummings	7148.003	7472

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EXAMINER	
RAMIREZ, DELIA M	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 06/15/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/661,049	CUMMINGS ET AL.	
	Examiner	Art Unit	
	Delia M. Ramirez	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6-15,17,18 and 21-23* is/are pending in the application.

4a) Of the above claim(s) *15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6-14,17,18 and 21-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 September 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/12/04,8/13/04*. 12/29/04
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *alignments*

DETAILED ACTION

Status of the Application

Claims 6-15,17,18 and 21-23 are pending.

Applicant's amendment of claims 17, 21, addition of new claims 22-23, and cancellation of claims 16, 19-20, as submitted in a communication filed on 3/29/2006 is acknowledged.

Applicant's election with traverse of Group V, claims 6-14, 17-18, 21 drawn to a polynucleotide comprising SEQ ID NO: 2, host cells, vectors, and a method to recombinantly produce the corresponding polypeptide, as submitted in a communication filed on 3/29/2006 is acknowledged.

Applicants traverse is on the ground(s) that (1) a search of all groups would not place an undue burden on the USPTO, and (2) the restriction places an excessive financial burden on Applicants. Applicants request that Groups V-VIII be rejoined for examination.

Applicant's arguments have been fully considered but are not deemed persuasive to withdraw the restriction requirement. The polynucleotides of SEQ ID NO: 2, 4, 6, 8 encode proteins isolated from different organisms (i.e., human, mouse, rat and *B. rerio*). An alignment of these polynucleotides show that these polynucleotides have different nucleotide sequences. Thus, a search of SEQ ID NO: 2 is not co-extensive to SEQ ID NO: 4, 6, and 8. A comprehensive search of Groups V-VIII would require a separate sequence search for each group in addition to patent/non-patent literature searches and class/subclass searches. Therefore, contrary to Applicant's assertions, a search of Groups V-VIII would impose an undue burden on the Office. With regard to arguments that the restriction places an excessive financial burden on Applicants, it is noted that issues related to the financial cost associated with filing patent applications are beyond the Examiner's authority.

The requirement is deemed proper and therefore is made FINAL.

Claim 15 is withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. New claims 22-23 are partially directed to the elected subject matter

(i.e., a polynucleotide comprising SEQ ID NO: 2, host cells, vectors, and a method to recombinantly produce the polypeptide of SEQ ID NO: 1). Claims 6-14, 17-18 and 21-23 are at issue and are being examined herein.

Specification

1. The use of the trademarks has been noted in this application. See, for example, "Bluescript" (page 19, paragraph [49]). They should be capitalized wherever they appear and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks. Applicants' cooperation is requested in reviewing the specification for other trademarks that may be present in the specification and making the appropriate correction(s).

2. The specification is objected to due to the recitation of "nepropathy" on page 38, paragraph [38]. This appears to be a typographical error. Appropriate correction is required.

Priority

3. Acknowledgment is made of a claim for domestic priority under 35 U.S.C. 119(e) to provisional application No. 60/411,310 filed on 09/13/2002.

4. It is noted that SEQ ID NO: 1-2 appear to have been disclosed in Figure 1 of provisional application No. 60/411,310.

Information Disclosure Statement

5. The information disclosure statements (IDS) submitted on 12/29/2004, 8/13/2004, and 3/12/2004 are acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Drawings

6. The drawings submitted on 9/12/2003 have been reviewed and are accepted by the Examiner.

Claim Objections

7. Claims 6-14, 18 are still partially directed to non-elected inventions (i.e., SEQ ID NO: 4, 6, 8). Examination of such claims will be restricted to the subject matter elected, which in the instant case is the polynucleotide of SEQ ID NO: 2, host cells, vectors, and method of recombinant production of the corresponding protein. Applicants are requested to amend the claims accordingly in response to this Office Action.

8. Claim 6 is objected to due to the recitation of "50 °C. And which has core...chaperone activity" for the following reasons. The period between 50 °C and the phrase "and which has core.." appears to be a typographical error. In addition, the term "And which ....chaperone activity" appears to be redundant in view of the fact that the preamble recites the function of the polypeptide encoded by the claimed polynucleotide. Also, as written, it appears as if the polynucleotide recited in item (B) is the one having that activity and not the polypeptide encoded by it. Appropriate correction is required.

Claim Rejections - 35 USC § 101

9. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

10. Claims 6-7 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claims 6-7, as written, do not sufficiently distinguish over nucleic acids as they exist naturally because the claims do not particularly point out any non-naturally occurring differences between the claimed products and the naturally occurring products. In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. See *Diamond v. Chakrabarty*, 447 US 303, 206 USPQ 193 (1980). The claims should be amended to indicate the hand of the inventor, e.g., by insertion of "isolated" or "purified" as taught by pages 40-41, paragraphs [103]-[105], of the specification. See MPEP 2105.

Claim Rejections - 35 USC § 112, Second Paragraph

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 6-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

13. Claim 6 (claims 7-14 dependent thereon) is indefinite in the recitation of "(C) a polynucleotide which differs....from the isolated polynucleotides of (A)" in view of the fact that there is no antecedent basis for "the isolated polynucleotides of A". For examination purposes, it will be assumed that the term recites "(C) a polynucleotide which differs....from the polynucleotide of (A)". Correction is required.

Claim Rejections - 35 USC § 112, First Paragraph

14. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

15. Claims 6-14, 17-18, 21-23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 6-8 are directed in part to a genus of polynucleotides encoding any chaperone of any core 1 β3-galactosyl transferase, wherein the polynucleotides (i) comprise any fragment of the coding region of the polynucleotide of SEQ ID NO: 2, (ii) hybridize to any fragment of the coding region of the polynucleotide of SEQ ID NO: 2 under the specific conditions recited, (iii) encode a soluble chaperone and share no structural element with the polynucleotide of SEQ ID NO: 2. As stated in MPEP 2111.01, during examination, the claims must be interpreted as broadly as their terms reasonably allow. In the absence of a definition of the term in the specification, the term "coding portion" as recited in item (A) of claim 6 has been interpreted as "any fragment within the coding region". Also, it is noted that the genus of polynucleotides of claim 6 (D) encoding soluble chaperones encompasses polynucleotides having no structural element in common with the polynucleotide of SEQ ID NO: 2 when (1) the fragment of the coding region of the polynucleotide of SEQ ID NO: 2 is within the transmembrane domain, or (2) hybridization occurs with a fragment of the polynucleotide of SEQ ID NO: 2 which is within the transmembrane domain. Claims 9-12 are directed in part to host cells transformed/transfected with a vector comprising the genus of polynucleotides described above. Claims 13-14 are directed in part to a process for recombinantly producing the genus of chaperones encoded by the genus of nucleic acids described above. Claim 17 is directed to an expression system comprising a host cell comprising a genus of polynucleotides encoding (1) any core 1 β3-galactosyl transferase, and (2) any chaperone of said core 1 β3-galactosyl transferase. Claim 18 is directed in part to the expression system of claim 17 wherein the polynucleotides encoding the chaperone comprise any fragment of the coding region of the

polynucleotide of SEQ ID NO: 2. It is noted that the Examiner has broadly interpreted the term "a coding sequence of SEQ ID NO: 2" as "any fragment within the coding sequence of polynucleotide of SEQ ID NO: 2". Claim 21 is directed to a host cell comprising a genus of polynucleotides encoding a chaperone of any core 1 β3-galactosyl transferase. Claims 22 and 23 are directed to the subject matter of claims 17 and 21, respectively, wherein the chaperone is mammalian.

In *University of California v. Eli Lilly & Co.*, 43 USPQ2d 1938, the Court of Appeals for the Federal Circuit has held that "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials". As indicated in MPEP § 2163, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show that Applicant was in possession of the claimed genus. In addition, MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

In the instant case, the claims require a large genus of polynucleotides for which there is no structural limitation wherein the polynucleotides are functionally related by encoding polypeptides from any source (1) having core 1 β3-galactosyl transferase activity, or (2) which are chaperones of any core 1 β3-galactosyl transferase. While the specification discloses the polypeptide of SEQ ID NO: 1 as being a chaperone of a human core 1 β3-galactosyl transferase known in the art, the specification fails to disclose (1) the structure of all chaperones of core 1 β3-galactosyl transferases, (2) the structure of all core 1 β3-

galactosyl transferases, (3) which are the structural elements required in any chaperone of a core 1 β3-galactosyl transferase or any core 1 β3-galactosyl transferase, (4) which are the structural elements in the polypeptide of SEQ ID NO: 1 which are essential for being a chaperone of a core 1 β3-galactosyl transferase activity, and which ones can be modified, (5) a correlation between structure and being able to act as a chaperone of a core 1 β3-galactosyl transferase, (6) a correlation between structure and core 1 β3-galactosyl transferase activity, or (7) a correlation between the structure of a core 1 β3-galactosyl transferase and a chaperone of said transferase such that one could determine the structure of the chaperone based on the structure of the core 1 β3-galactosyl transferase. Furthermore, the specification is completely silent in regard to the structural elements found in the polynucleotide of SEQ ID NO: 2 required in any nucleic acid encoding a mammalian chaperone of a core 1 β3-galactosyl transferase.

The claims encompass genera of polynucleotides which are structurally unrelated. A sufficient written description of a genus of polynucleotides may be achieved by a recitation of a representative number of polynucleotides defined by their nucleotide sequence or a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus. However, in the instant case, either there is no structural feature which is representative of all the members of the genus of polynucleotides recited in the claims, or the structural features recited/interpreted (i.e., "a fragment of the polynucleotide of SEQ ID NO: 2", "hybridizes with a fragment of the polynucleotide of SEQ ID NO: 2") do not constitute a substantial portion of the genus as the remainder of the structure of any nucleic acid encoding a chaperone of a core 1 β3-galactosyl transferase is completely undefined and the specification does not define the remaining structural features necessary for members of the genus to be selected.

While one could argue that the structures disclosed in the specification and the prior art are representative of the structure of all the members of the genus of polynucleotides recited, it is noted that the art teaches several examples of how even small variations in structure result in functional variations.

For example, Witkowski et al. (Biochemistry 38:11643-11650, 1999) teaches that one conservative amino acid substitution transforms a β-ketoacyl synthase into a malonyl decarboxylase and completely eliminates β-ketoacyl synthase activity. Seffernick et al. (J. Bacteriol. 183(8):2405-2410, 2001) teaches that two naturally occurring *Pseudomonas* enzymes having 98% amino acid sequence identity catalyze two different reactions: deamination and dehalogenation, therefore having different function. Therefore, since minor structural variations may result in variations affecting function, and no additional information correlating structure with (1) core 1 β3-galactosyl transferase activity, or (2) the ability to be a chaperone of a core 1 β3-galactosyl transferase has been provided, one cannot reasonably conclude that the structures disclosed in the specification and/or the prior art are representative of the structure of all the polynucleotides as recited in the claims.

Due to the fact that the specification only discloses a few species of polynucleotides encoding chaperones of a core 1 β3-galactosyl transferase, and the lack of description of any additional species by any relevant, identifying characteristics or properties, one of skill in the art would not recognize from the disclosure that Applicant was in possession of the claimed invention.

16. Claims 6-14, 17-18, 21-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a polynucleotide comprising SEQ ID NO: 2, isolated host cells and vectors comprising said polynucleotide, and a method to recombinantly produce the polypeptide of SEQ ID NO: 1, does not reasonably provide enablement for (1) any polynucleotide encoding a chaperone of a core 1 β3-galactosyl transferase, wherein said polynucleotide (i) can have any structure, (ii) comprises any fragment of the polynucleotide of SEQ ID NO: 2, (iii) hybridizes to any fragment of the polynucleotide of SEQ ID NO: 2, (2) vectors and host cells (isolated and non-isolated) comprising the polynucleotide of (1), (3) a method to recombinantly produce the polypeptide encoded by the polynucleotide of (1), or (4) a host cell (isolated and non-isolated) comprising a polynucleotide encoding

any core 1 β3-galactosyl transferase, and a polynucleotide encoding any chaperone of a core 1 β3-galactosyl transferase. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2nd 1400 (Fed. Cir. 1988)) as follows: (1) quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence and absence of working examples, (4) the nature of the invention, (5) the state of prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breath of the claims. The factors which have lead the Examiner to conclude that the specification fails to teach how to make and/or use the claimed invention without undue experimentation, are addressed in detail below.

The breath of the claims. Claims 6-14, 17-18, 21-23 are so broad as to encompass (1) polynucleotides encoding any chaperone of any core 1 β3-galactosyl transferase, wherein the polynucleotides (i) comprise any fragment of the coding region of the polynucleotide of SEQ ID NO: 2, (ii) hybridize to any fragment of the coding region of the polynucleotide of SEQ ID NO: 2 under the specific conditions recited, (iii) encode a soluble chaperone and share no structural element with the polynucleotide of SEQ ID NO: 2, (2) host cells transformed/transfected with a vector comprising the polynucleotides of (1), or host cells comprising a polynucleotide encoding any chaperone (or any mammalian chaperone) of a core1 β3-galactosyl transferase, (3) a process for recombinantly producing the chaperones encoded by the polynucleotides of (1), and (4) an expression system comprising a host cell comprising polynucleotides encoding (i) any core 1 β3-galactosyl transferase, and (ii) any chaperone of said core 1 β3-galactosyl transferase. See Claim Rejections under 35 USC 112, first paragraph (written description) for discussion on claim interpretation and scope.

The enablement provided is not commensurate in scope with the claims due to the extremely large number of polynucleotides of essentially unknown structure encompassed by the claims. In the instant case, the specification enables the polynucleotide of SEQ ID NO: 2.

With regard to claims 9-12, 17-18, 21-23, it is noted that the specification discloses that one of the intended uses for the polynucleotides of the invention is to create *in vivo* mutations (paragraph [84]) and as therapy in the treatment of Tn-syndrome and IgA nephropathy syndrome (paragraphs [97]-[98]). Thus, it appears that the specification contemplates using the polynucleotides of the invention in gene therapy and possibly in the generation of transgenic animals. Therefore, in its the broadest reasonable interpretation, claims 9-12, 17-18, 21-23 encompass not only to isolated host cells but also to host cells within a transgenic multicellular organism (i.e., non-isolated). The enablement provided is not commensurate in scope with the claim due to the extremely large number of transgenic multicellular organisms comprising the recited cells encompassed by the claims which the specification fails to teach how to generate or how to use, as well as the lack of information as to how to deliver the recited polynucleotides to a human being such that expression of said polynucleotides would occur. In the instant case, the specification enables an isolated host cell comprising the polynucleotide of SEQ ID NO: 2.

The amount of direction or guidance presented and the existence of working examples. The specification discloses the nucleotide sequence of the polynucleotide of SEQ ID NO: 2, as well as the amino acid sequence of the polypeptide of SEQ ID NO: 1 as working examples. The specification also discloses three additional chaperones from other organisms. However, the specification fails to provide (1) the structure of additional chaperones of core 1 β3-galactosyl transferases, or additional core 1 β3-galactosyl transferases, (2) the structural elements required in any chaperone of a core 1 β3-galactosyl transferase, or in any core 1 β3-galactosyl transferase, (3) fragments of the polypeptide of SEQ ID NO: 1 which correlate with being a chaperone of a core 1 β3-galactosyl transferase, (4) a correlation between

structure and being able to act as a chaperone of a core 1 β3-galactosyl transferase, (5) a correlation between structure and core 1 β3-galactosyl transferase activity, (6) a correlation between the structure of a core 1 β3-galactosyl transferase and a chaperone of said transferase such that one could envision the structure of the chaperone based on the structure of the core 1 β3-galactosyl transferase, or (7) which are the structural elements found in a mammalian chaperone of a core 1 β3-galactosyl transferase not present in chaperones from other sources. Thus, there is no information or guidance such that one of skill in the art can create/isolate the entire genus of polynucleotides recited without undue experimentation.

With regard to claims 9-12, 17-18, 21-23, while the specification discloses that the polynucleotides of the invention can be used to transform host cells for recombinant production of the corresponding polypeptides, to create *in vivo* mutations, and for therapy, there are no working examples or specific methods disclosed showing how to create *in vivo* mutations in any multicellular organism. Also, there are no working examples or specific methods disclosed showing how to deliver the recited genus of polynucleotides to human tissues such that the recited polynucleotides can be expressed.

The state of prior art, the relative skill of those in the art, and the predictability or unpredictability of the art. The nucleotide sequence of the coding region of a polynucleotide encoding a protein determines the structural and functional properties of that protein. In the instant case, neither the specification nor the art provide a correlation between structure and activity such that one of skill in the art can envision the structure of any nucleic acid encoding a polypeptide having the same biological function as that of the polypeptide of SEQ ID NO: 1. Furthermore, there is no correlation between structure and core 1 β3-galactosyl transferase activity such that one can envision the structure of any nucleic acid encoding a core 1 β3-galactosyl transferase. In addition, the art does not provide any teaching or guidance as to (1) which nucleotides in the polynucleotide of SEQ ID NO: 2 can be modified and which ones are conserved such that one of skill in the art can make variants as recited encoding polypeptides with the same biological activity as that of the polypeptide of SEQ ID NO: 1, (2) which

segments of the polypeptide of SEQ ID NO: 1 or the polynucleotide of SEQ ID NO: 2, are essential for activity, and (3) the general tolerance of chaperones of core 1 β3-galactosyl transferases and core 1 β3-galactosyl transferases to structural modifications and the extent of such tolerance. The art clearly teaches that changes in a protein's amino acid sequence to obtain the desired activity without any guidance/knowledge as to which amino acids in a protein are required for that activity is highly unpredictable. At the time of the invention there was a high level of unpredictability associated with altering a polypeptide sequence with an expectation that the polypeptide will maintain the desired activity. For example, Branden et al. (Introduction to Protein Structure, Garland Publishing Inc., New York, page 247, 1991) teach that (1) protein engineers are frequently surprised by the range of effects caused by single mutations that they hoped would change only one specific and simple property in enzymes, (2) the often surprising results obtained by experiments where single mutations are made reveal how little is known about the rules of protein stability, and (3) the difficulties in designing *de novo* stable proteins with specific functions. The teachings of Branden et al. are further supported by the teachings of Witkowski et al. and Seffernick et al. already discussed above, where it is shown that even small amino acid changes result in enzymatic activity changes.

With regard to transgenic multicellular organisms, the prior art teaches that making genetically modified animals is highly unpredictable. The relevant art has for many years indicated that the unpredictability of generating transgenic animals lies with the site or sites of integration of the transgene into the target genome. Kappel et al. (Current Opinion in Biotechnology 3:548-553, 1992) teach that transgenic animals are known to have inherent cellular mechanisms which may alter the pattern of gene expression, such as DNA methylation or deletion from the genome (page 549, right column, third paragraph). Furthermore, Mullins et al. (Hypertension 22(4):630-633, 1993) teach that integration of a transgene in different species may result in widely different phenotypic responses (page 631, left column, first paragraph, last sentence). Also, Mullins et al. (J. Clin. Invest. 97(7):1557-1560, 1996) teach that "the

use of nonmurine species for transgenesis will continue to reflect the suitability of a particular species for the specific questions being addressed, bearing in mind that a given construct may react very differently from one species to another." (page 1559, Summary). Wigley et al. (Reprod. Fert. Dev. 6:585-588, 1994) indicate that transgenesis by microinjection has a number of limitations including random integration in the genome and integration of transgenes in multiple copies at one site such that expression level is not proportional to transgene copy number (page 585, Introduction). Cameron (Molecular Biotechnology 7:253-265, 1997) teaches that well-regulated expression of the transgene is not frequently achieved because of poor levels or the complete absence of expression or leaky expression in non-target tissues (page 256, left column, last three lines, right column, first three lines). According to Cameron, transgene expression with different transgenic lines produced with the same constructs is unpredictable and expression levels do not correlate with the number of transgene copies integrated, thus indicating the influence of the integration site on the expression pattern (page 256, right column, lines 3-13).

In regard to DNA delivery and expression in human tissues, the art teaches the high unpredictability of delivering DNA to human tissues and achieving the desired expression. For example, Phillips (J. Pharm. Pharmacology 53:1169-1174, 2001) teaches that the major challenges in gene therapy have been delivery of DNA to target cells and duration of expression (Abstract). According to Phillips, the problem regarding gene therapy is twofold in that (1) a system must be design to deliver DNA to a specific target while preventing degradation within the body, and (2) an expression system must be built into the DNA construct to allow the target cell to express the protein at therapeutic levels for a determined amount of time (page 1170, left column, lines 7-15). Gardlik et al. (Med. Sci. Monit. 11(4):RA110-121, 2005) teach that (1) while there are a number of methods known for delivery of DNA, there is no clear ideal delivery system (RA119, last paragraph), and (2) the main problem in gene therapy lies in the secure and efficient delivery of genes into target cells and tissues (RA110, Summary).

The quantity of experimentation required to practice the claimed invention based on the teachings of the specification. While methods of generating or isolating variants of a polynucleotide were known in the art at the time of the invention, it was not routine in the art to screen by a trial and error process for all polynucleotides encoding chaperones of any core 1 β3-galactosyl transferase, or all polynucleotides encoding core 1 β3-galactosyl transferases. In the absence of (1) a rational and predictable scheme for modifying any nucleotide in the polynucleotide of SEQ ID NO: 2 such that the resulting variant would encode a protein which retains the same activity as that of the polypeptide of SEQ ID NO: 1, and/or (2) a correlation between structure and (i) being a chaperone of any core 1 β3-galactosyl transferase, or (ii) core 1 β3-galactosyl transferase activity, one of skill in the art would have to test an essentially infinite number of polynucleotides to determine which ones encode chaperones of core 1 β3-galactosyl transferases, or core 1 β3-galactosyl transferases.

While the skilled artisan can produce variants of the polynucleotide of SEQ ID NO: 2 having the recited structural characteristics using well-known and widely used in the art, the number of polynucleotides to be tested for the desired activity is essentially infinite. While current screening techniques in the art would allow for testing a limited number of species, testing an infinite number of species would not be possible. Therefore, while enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, as is the case herein, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed so that a reasonable number of species can be selected for testing. In view of the fact that such guidance has not been provided in the instant specification, it would require undue experimentation to enable the full scope of the claims.

Furthermore, given the teachings of the art regarding the differences in expression of a transgene in different species, the limitations regarding the integration and expression of a transgene, the unpredictability of delivering and expressing DNA in human tissues, and in view of the lack of guidance

provided by the specification, it would have required undue experimentation to engineer any transgenic multicellular organism, or cells thereof, as claimed.

Therefore, taking into consideration the extremely broad scope of the claims, the lack of guidance, the amount of information provided, the lack of knowledge about a correlation between structure and function, the high degree of unpredictability of the prior art in regard to (a) structural changes and their effect on function, (b) generation of transgenic multicellular organisms, and (c) delivery and expression of DNA in human tissues, one of ordinary skill in the art would have to go through the burden of undue experimentation in order to practice the claimed invention. Thus, Applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the invention in a manner reasonably correlated with the scope of the claims.

Claim Rejections - 35 USC § 102

17. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

18. Claims 6-10, 13-14, 21, 23 are rejected under 35 U.S.C. 102(b) as being anticipated by Chen et al. (WO 00/15796 published on March 23, 2000).

Claims 6-7 are directed in part to DNA molecules encoding any chaperone of any core 1 β3-galactosyl transferase, wherein the DNA molecules (i) comprise any fragment of the coding region of the polynucleotide of SEQ ID NO: 2, (ii) hybridize to any fragment of the coding region of the polynucleotide of SEQ ID NO: 2 under the specific conditions recited, (iii) encode a soluble chaperone and share no structural element with the polynucleotide of SEQ ID NO: 2. See Claim Rejections under 35 USC 112, first paragraph (written description) for claim interpretation and scope. Claim 8 is directed

to a vector comprising the DNA molecules of claim 6. Claims 9-10 are directed in part to host cells transformed/transfected with an expression vector (i.e. comprising an expression control sequence). Claim 13-14 are directed in part to a method to recombinantly produce the polypeptides encoded by the DNA molecules of claim 6 wherein the polypeptides are soluble. Claims 21 and 23 are directed in part to a host cell comprising any polynucleotide encoding a mammalian chaperone of a core 1 β3-galactosyl transferase.

Chen et al. teach a human polypeptide which is identical to the polypeptide of SEQ ID NO: 1 (318 amino acids; PRO310; SEQ ID NO: 341; Figure 120) as well as its cDNA (1572 base pairs; SEQ ID NO: 340; page 55, lines 10-25; Figure 119). The cDNA of Chen et al. comprises all of SEQ ID NO:1. See attached alignments provided for visualization purposes. Chen et al. also teach the PRO310 polynucleotide lacking the section coding for the transmembrane domain (page 56, lines 18-32; page 57, lines 24-28) and thus coding for a soluble protein, expression vectors and host cells comprising the polynucleotide, as well as a method for recombinantly producing the PRO310 polypeptide with and without the transmembrane domain (page 56, lines 1-5; page 99, line 1-page 102, line 35). The polypeptide of Chen et al. would inherently have the ability to act as a chaperone of a core 1 β3-galactosyl transferase as it is identical to the polypeptide of SEQ ID NO: 1 described in the specification as having that activity. Thus, the teachings of Chen et al. anticipate the instant claims as written.

It is noted that due to the length of the WIPO document (over 300 pages), only relevant pages are being submitted with this Office action.

Conclusion

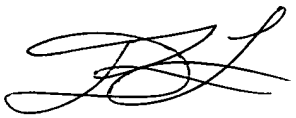
19. No claim is in condition for allowance.

20. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PMR) system. Status information for published applications may be obtained from

either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (571) 272-0938. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (571) 272-0928. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.



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Art Unit 1652

DR
June 9, 2006